REMARKS

Claims 59-116 are pending in this application. By this amendment, claims 62 and 103 are cancelled without prejudice or disclaimer, and claims 59, 63, 66, 71, 72, 76, 79, 108, 109, and 115 are amended. Following entry of this amendment, claims 59-61, 63-102, and 104-116 will be pending. Entry of this amendment is respectfully requested.

In addition to the amendments discussed below, Applicants note that claim 63 is amended and now recites "the first selectable gene of the fusion gene" (rather than "the first selectable gene of the fusion") to improve the consistency of claim language. This is a non-narrowing amendment. Claim 76 is amended and now recites "cytomegalovirus (CMV)" (rather than "CMV"). This is a non-narrowing amendment. Claim 79 is amended and now recites "CMV" (rather than "cytomegalovirus"). This is a non-narrowing amendment. Support for the amendments and new claims is found throughout the specification and originally filed claims, including, e.g., specification at original claim 62, page 12, lines 2-4, and Figure 7. No new matter is added by this amendment.

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any objection and/or rejection made by the Office. Applicants expressly reserve the right to pursue prosecution of any subject matter not presently claimed in one or more future or pending continuation and/or divisional applications.

Request for rejoinder of withdrawn claims

Applicants respectfully request rejoinder of withdrawn process claims that depend from or otherwise include all of the limitations of allowable product claims, in accordance with the provisions of MPEP § 821.04.

Information Disclosure Statements

Applicants thank the Examiner for considering and initialing the PTO Forms 1449 that were mailed with the Office Action. Applicants note that a Supplemental Information Disclosure statement was mailed February 2, 2006. Consideration of the references submitted therein and return of an initialed PTO Form 1449 is respectfully requested.

Allowed Claims

Applicants note with appreciation that claims 102 and 104 have been indicated as allowable if rewritten in independent form with all intervening claimed limitations.

Specification

The specification is amended to replace "Figure 9" with "Figure 1" at page 25, lines 21 and 23, page 27, line 35, and page 28, lines 3, 21, and 31. Applicants submit that these references to "Figure 9" are obvious typographical errors for at least the following reasons. First, the paragraphs in which the correction has been made refer to "structures" and "configurations" of exemplary polynucleotide constructs. Figure 1 shows 9 exemplary construct designs. By contrast, Figure 9 depicts graphs showing "DNase productivity vs. GFP productivity" and "DNase RNA vs. DNase productivity". Second, the corrected sentences in the specification refer to line numbers within the figure. Figure 1 contains 9 numbered lines within the figure. By contrast, Figure 9 shows two graphs and does not have any numbered lines. Thus it is evident that one of ordinary skill would understand that these references to Figure 9 are obvious typographic errors, and that Figure 1 should be referenced instead. Accordingly, no new matter is added by the amendments, and entry of the amendments is respectfully requested.

Sequence Compliance

The Office Action states that Figures 13A and 13B disclose amino acid sequences that are not properly identified with sequence identifiers. Applicants note that the figure legend for Figure 13 states

> Figure 13 shows the amino acid sequences of the full length heavy (Fig. 13A; SEQ ID NO. 1) and light chains (Fig. 13B;SEQ ID NO. 2) of the anti-IgE antibody, E26.
> Specification, page 7, lines 24-25.

Accordingly, the amino acid sequences of Figures 13A and B have been properly identified with sequence identifiers. Withdrawal of the request for sequence compliance is respectfully requested.

Objections

Claims 106, 108 and 109 are objected to under 37 CFR 1.75(c) as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim.

Applicants respectfully disagree that the rejected claims fail to further limit the subject matter of a previous claim, since claims 106, 108 and 109 clearly recite an additional limitation not found in the parent claim. However, to expedite prosecution, claims 106, 108 and 109 have been amended consistent with the Examiner's suggestion, and now recite "wherein the first selectable gene encodes puromycin resistance and the amplifiable second gene encodes DHFR", or "wherein the first selectable gene encodes puromycin resistance and the amplifiable second gene encodes DHFR". Withdrawal of this objection is respectfully requested.

Claim 71 is objected to under 37 CFR 1.75(c) as allegedly informal on the ground that the claim would be "more precise" if the term "positioned" were inserted before the term "between" to remove any potential ambiguity. Applicants have amended the claim as suggested by the Examiner. Withdrawal of this objection is respectfully requested.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 88, 97, 103 and 115 are rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. Applicants respectfully traverse this rejection.

Claims 88, 97, and 115 are rejected on the ground that the phrase "the amplifiable selectable gene" allegedly lacks sufficient antecedent support. Applicants respectfully traverse this rejection. Lack of antecedent basis does not always result in claim indefiniteness, see, e.g., MPEP Section 2173.05(e), and Applicants respectfully submit that one of ordinary skill could readily ascertain the scope of the rejected claims. However, to expedite prosecution, claims 88 and 97 have been amended and now recite "the amplifiable second selectable gene", consistent with the Examiner's suggestions. Withdrawal of this rejection is respectfully requested.

Claim 103 is rejected as allegedly indefinite on the ground that use of the trademark/tradename HERCEPTIN renders the claim indefinite. Claim 103 has been cancelled, rendering this rejection moot. Withdrawal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. § 102(e), or in the alternative, 35 U.S.C. § 103(a)

102(e)

Claims 59-66, 80-81, 84-87, 89-90 and 115 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Herlitschka, et al. (US 6,114,146) ("Herlitschka"). Applicants respectfully traverse this rejection.

As a preliminary matter, Applicants note that claims 59 and 72 have been amended and now clarify that the first selectable gene is not amplifiable.

A prima facie case of anticipation has not been made because Herlitschka does not teach a polynucleotide comprising, in operable linkage (a) a fusion gene comprising a first selectable gene and an amplifiable second selectable gene; (b) a selected sequence encoding a desired product; and (c) a promoter, wherein the first selectable gene is not amplifiable.[1]

By contrast, Herlitschka discloses a vector comprising a fusion gene encoding two amplifiable selectable markers: DHFR and *hph*, the gene encoding resistance to hygromycin. Herlitschka teaches that this system permits use of methotrexate as a dominant selectable marker in dhfr+ cells, which Herlitschka characterizes as a previously unaddressed problem.

Specifically, Herlitschka teaches that:

> [a] surprising result was obtained that also the hygromycin B phosphotransferase gene is amplifiable. (Emphasis added; col. 8, lines 9-11)
>
> and
>
> [t]he dihydrofolate reductase gene/hygromycin B phosphotransferase gene system offers the particular advantage that on account of the tight coupling of the hph and dhfr domains, this fusion protein can be amplified as a dominant marker also in cells having endogenous dhfr gene. This is particularly enabled by the property of hph amplification potential so that one can speak of a double-dominant selectable and double amplifiable marker protein. (Emphasis added; col. 6, lines 20-27)
>
> and
>
> at first a sufficiently high hph amplification can be effected which ensures in the subsequence switching to MTX that the MTX concentration which is selected then, can no longer by compensated by endogenous DHFR. (Emphasis added; col. 6, lines 27-31).

Applicants acknowledge that Herlitschka mentions a "selection marker" in the specification. But the only disclosure in Herlitschka of "selection markers" suitable for use in the invention is *hph*, and Herlitschka explicitly states that *hph* is an amplifiable selection marker. Accordingly, it is evident that Herlitschka discloses a vector comprising a fusion gene encoding two amplifiable selectable markers. A vector comprising a fusion gene encoding two amplifiable

[1] For the record, Applicants additionally note that in the rejection, the Examiner cites to portions of the background section rather than the disclosure of Herlitschka's technology in several instances: col. 5, lines 1-8 is cited for the proposition that Herlitschka teaches that expression vectors can be utilized to transform CHO cells. By contrast, col. 5, lines 1-8 discusses the disclosure of background document EP 0 351 586-A). In addition, col. 5, line 15 is cited for the teaching of DHFR deficient CHO cells. By contrast, col. 5, line 15 discusses the disclosure in background document Kaufman et al JBC 261:9622). Applicants submit that references to disclosure in background documents do not constitute a teaching relating to Herlitschka's vectors.

selectable markers does not anticipate the present claims to a polynucleotide comprising, in operable linkage, (a) a fusion gene comprising a first selectable gene and an amplifiable second selectable gene; (b) a selected sequence encoding a desired product; and (c) a promoter, wherein the first selectable gene is not amplifiable. Withdrawal of this rejection is respectfully requested.

Regarding the rejection of claim 80, Applicants respectfully disagree with the Examiner's overbroad interpretation of the term receptor. Applicants submit that one of skill in the art would not interpret the term "receptor" to encompass Factor VIII, a secreted glycoprotein found in plasma. Accordingly, a prima facie case has not been made, and withdrawal of this rejection is respectfully requested.

103(a)

Claims 59-66, 80-81, 84-87, 89-90 and 115 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Herlitschka, et al. (US 6,114,146) ("Herlitschka"). Applicants respectfully traverse this rejection.

A prima facie case of obviousness has not been made. To establish a prima facie case of obviousness, three basic criteria must be met. First, the prior art reference(s) must teach or suggest all the claim limitations. Second, there must be some suggestion or motivation to modify the reference or to combine reference teachings. Third, there must be a reasonable expectation of success. See M.P.E.P. § 2143. Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the Applicants' disclosure. See In re Vaeck, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

The Examiner has not demonstrated that Herlitschka teaches or suggests all the claim limitations, as noted above in response to the rejection under 35 U.S.C. § 102(e). Nor has the Examiner explained how Herlitschka might be modified, such that Herlitschka renders the present claims obvious. Finally, the Examiner has not explained how there might be a reasonable expectation of success. Thus, a prima facie case of obviousness has not been made, and withdrawal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. § 103(a)

Claims 65, 88, 103, 106 and 107 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Herlitschka, et al. (US 6,114,146) and further in view of Levenson, et al. (Hum. Gene. Ther. 1998; 9:1233-36) ("Levenson") and Keyt, et al. (J.Biol. Chem. 1996; 271:5638-46)("Keyt"). Applicants respectfully traverse this rejection.

A prima facie case of obviousness has not been made. Herlitschka does not teach each and every limitation of the rejected claims, as noted above. Levenson and Keyt do not remedy Herlitschka's deficiencies.

In the Office Action, Levenson is cited as allegedly disclosing:

> expression vectors containing GFP, puromycin, as well as hygromycin B, which are utilized in a dicistronic vector that is used to transform mammalian cells and expression [sic] a gene of interest encoding a desired protein. (Office Action, page 7)

and that

> it would be obvious to modify the vector that the '146 patent teaches with alternative antibiotic resistance gene(s), such as puromycin, or alternatively to incorporate a fluorescent marker. (Office Action, page 7).

As a preliminary matter, Applicants note that the vectors of Levenson are monocistronic vectors (termed "single transcript vectors" or "STVs" by Levenson), not dicistronic vectors as stated in the Office Action. *See* Levenson, page 1233, left column (describing single transcript vectors in which a single promoter drives the expression of both genes, and stating that the present study related to a family of retroviral IRES-STVs). Thus, Levenson does not disclosure use of antibiotic resistance genes or fluorescent markers in a dicistronic vector, as stated by the Examiner.

Moreover, Applicants submit that one of ordinary skill in the art would lack motivation to substitute non-amplifiable selectable markers, such as puromycin acetyltranferase and GFP, into the vector of Herlitschka, since Herlitschka describes vectors comprising two amplifiable selectable markers. Accordingly, Applicants submit that a prima facie case of obviousness has not been made. Withdrawal of this rejection is respectfully requested.

Keyt is cited as allegedly disclosing expression vectors encoding VEGF and variants thereof. (Office Action, page 8). However, Keyt does not disclose the claimed polynucleotides. Accordingly, Applicants submit that a prima facie case of obviousness has not been made. Withdrawal of this rejection is respectfully requested.

Double Patenting Rejection

Claims 59-90, 93-99, 105-111, 113 and 115-116 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly obvious over claims 106-118, 122-152 and 161-164 of co-pending Application No. 10/019,586 (" '586 application")

in view of Levenson, et al. (Hum. Gene. Ther. 1998; 9:1233-36). Applicants respectfully traverse this rejection for the reasons stated below. However, Applicants additionally request that this provisional rejection be placed in abeyance until allowable subject matter has been found.

A prima facie case of obviousness-type double patenting has not been made. In an obviousness-type double patenting analysis, the Examiner must compare what is defined by the claims of the later application against what is defined by the claims of the earlier application. This analysis must be based on the claims as a whole, not one feature or element of the claims considered in isolation. *See, e.g. General Food Corp. v Studiengesellschaft Kohl mbH*, 972 F2d 1272, 1278-79 (Fed. Cir. 1992 ("Claims must be read as a whole in analyzing a claim of double patenting"); *Eli Lilly v Barr Labs, Inc.*, 251 F3d 955, 972 (Fed. Cir. 2001) ("We compared the differences between the claims at issue as a whole and conclude that they are not patentably distinct") (emphasis added). In other word, the compositions and methods as defined by *all the required* limitations of the claims of the '586 application must be compared to the compositions and methods as defined by *all the required* limitations of the claims of the instant application.

It is improper to compare only one step or limitation found in claims of the instant application and claims of the '586 application, and to ignore additional limitations required by the claims of the instant application.

The Examiner did not compare the claims as a whole

The Examiner has not explained why the inventions defined by claims 59-90, 93-99, 105-111, 113 and 115-116 would be considered "obvious" in view of the inventions defined by claims 106-118, 122-152 and 161-164 of the '586 application. Instead, the Examiner relied upon the comparison of individual steps or limitations found in the independent claims of the instant application and the independent claims of the '586 application (eg, vector and polynucleotide, GFP and selectable gene), concluding that

> [i]n general, the reference claims represent a species of the broader instant genus claims, and both sets of claims are directed to polynucleotides, cells transformed with said polynucleotides and utilizing said compositions to produce desired proteins. (Office Action, page 9).

and

> [i]n sum, but for the slight modifications of polynucleotide versus [sic] vector and GFP versus [sic] selectable gene, the instant and reference claims are not patentable distinguishable. (Office Action, page 11).

Because the Examiner did not compare the claims as a whole, and instead compared features or elements of the claims considered in isolation, a *prima facie* case of obviousness-type double patenting has not been made. Withdrawal of this rejection is respectfully requested.

The claims of the instant application require an additional limitation not found in certain rejected claims of the '586 application

Applicants note for the record that comparison of the rejected claims of the instant application and claims 112-118, 122-127, 130-147, 151-152 and 161-164 of the '586 application reveals that the claims of the instant application require "a fusion gene comprising a first selectable gene and an amplifiable second selectable gene". This limitation is not present in claims 112-118, 122-127, 130, 132-142, 151-152 and 161-164 of the '586 application.

In the rejection, the Examiner did not explain how claims in the '586 application that lack the requirement of "a fusion gene comprising a first selectable gene and an amplifiable second selectable gene" allegedly render obvious the rejected instant claims, which do require "a fusion gene comprising a first selectable gene and an amplifiable second selectable gene". Accordingly, Applicants submit that this rejection is improper. Withdrawal of this rejection is respectfully requested.

The Examiner relies on Levenson for the proposition that ""puromycin is one of several selectable markers that are routinely utilized in the art of dicistronic vectors and protein expression in mammalian cells". As noted above, Levenson concerns monocistronic vectors. Thus, Applicants submit that Levenson is not relevant to the present rejection. Withdrawal of this rejection is respectfully requested.

Finally, Applicants note that the Examiner does not provide a rationale for the rejection of claims 77, 79, 80-81, 86-69, 105-111, 113, and 115-116. Accordingly, the rejection of these claims is improper and should be withdrawn. The Examiner also fails to discuss claims 114, 116-118, 122-127, 129-134, 144-147, 150, 152, 162 and 162 of the '586 application, thus making it unclear why these claims are relied upon in the rejection.

For the above-stated reasons, withdrawal of this rejection is respectfully requested.

SUMMARY

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is strongly encouraged to call the undersigned at the number indicated below.

Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,
GENENTECH, INC.

Date: March 9 2006

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